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Epizootic Rabbit Enteropathy (ERE): A Review of Current Knowledge

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Abstract

This literature review deals with Epizootic rabbit enteropathy (ERE), a condition which is potentially fatal to infected animals and continues to threaten the rabbit production industry internationally. The documented history of the condition is reviewed, together with what is known regarding the aetiology of the disease and candidate organisms which appear to be associated with its onset, although cannot be implicated as being the causal agent. Approaches to reduce the incidence of the condition (combining both husbandry practices and nutritional considerations), together with potential post-onset treatments and management strategies are also discussed.

Keywords: Epizootic rabbit enteropathy (ERE); history; aetiology; bacteria; review

Introduction

General background

Epizootic rabbit enteropathy (ERE), which was originally called mucoid enteropathy (Flatt *et al.*, 1974) and more recently mucoid enteritis, is a digestive pathology. It mainly affects farmed rabbits in both intensive and semi-intensive systems, although there are also reports of ERE in pet rabbits these are considered to be rare (Haligur *et al*., 2009). Irrespective of geographic location, it has been known to have a negative impact on rabbit production since the 1990s (Licois *et al*., 1998; Le Bouquin *et al*., 2009), with as many as 95% of animals in any one rabbit production system affected,

resulting in levels of approximately 90% morbidity and 80% mortality (Licois *et al*., 2006).

While this is a disorder of the digestive tract, the impact of the disease can extend beyond digestive issues. Rabbits affected are between 3 and 7 weeks, and show a reduction in their daily feed intake of 50% going from 110g per day to 55g a day for approximately 7 days (Pérez de Rozas *et al*., 2005). Even in weaned animals there are reports suggesting morbidity losses. For example, enteritis has been shown to contribute to 10% to 20% losses, although there are cases where this can reach as high as 20% to 60% in mature animals (Cheeke, 1995; Olvera *et al*., 2008). Although ERE is not always fatal, rabbits that survive the disease have a lower weight compared to healthy rabbits in the same production system. These conditions cause a decrease in productivity, mainly due to growth retardation and low weight gain (Finzi *et al*., 1996; Pérez de Rozas *et al*., 2005). In turn, this leads to a decrease in the quantity of meat produced, and affects profit margins.

In addition to traits associated directly with digestion there have also been reports suggesting other factors can be affected. It has been shown that there can be as much as a 25% decrease in the fertility of rabbits and up to a 15% decrease in libido in affected males (Garcia *et al*., 2005; Pérez, 2013). The consequence of this is a decrease in the number of rabbits produced per cycle (Licois *et al.,* 2000; Fernández, 2006).

History and geographical spread of ERE.

There are conflicting reports in the scientific literature regarding the origins of ERE. The first potential report of the condition dates back over 100 years, based on a description of symptoms similar to ERE, albeit the term enteropathy was not used at that time. Mucoid enteropathy (Flatt *et al.*, 1974), one of the previous names used for the condition, has been known for over 40 years. However, the first definitive description of the condition dates back to ERE having emerged in both France at the end of 1996 (Licois *et al*., 2005) and Galicia in Spain in September 1996. In the case of Galicia, at least 700 farms were affected by the end of 1997 (Fernández, 2006). Monitoring of the development of the disease on French farms was carried out every 6 months from 1997 and revealed that from 1997 to 2002 more than 90% of French rabbit farms were affected by ERE, either at acute or latent levels. Within Europe it has since been reported in a number of other countries, including Britain, Portugal, Hungary and Belgium.

Although ERE as a condition in the current form was first documented in Europe, it is an international problem, with examples having been reported in other continents. For example, in Mexico the condition was first seen towards the end of 2001 and early 2002, affecting different production centres, but primarily in rabbits aged between 5 and 7 weeks (Rodríguez-De Lara *et al.*,

2008). As with other countries, the condition has persisted in Mexico, with recent studies reporting variable mortality levels in the range of 30 to 70% (Pérez, 2013), and an ERE incidence of around 31% (Pérez *et al.*, 2015).

Clinical signs of ERE.

The condition was first categorised as an enteropathy because it presented as a distension of the abdomen, generalised dilatation in the gastrointestinal tract, caecal paralysis in some cases and presence of abundant mucus (Licois *et al*., 2000). Due to the absence of macroscopic and histological lesions, (other than hyperplasia of the goblet cells in the small intestine), the term mucoid enteropathy was used. This was a reflection of observations that there was no visible inflammation of the intestine at the site of the mucoid enteritis (Allen and Bryant, 2009; Licois *et al*., 2005; Pérez de Rozas *et al*., 2005). However, ERE can be difficult to diagnose due to similarity of symptoms between it and other enteropathies (Licois *et al*., 2005).

During ERE outbreaks, rabbits reduce their level of intake of food and water, and in extreme cases will stop eating and drinking. This can lead to both dehydration and weight loss. The affected rabbits show a distended abdomen, with mild and minor diarrhoea and translucent mucus (Dewrée et al., 2007; Pérez, 2013). Following necropsy of animals which died of the condition, the stomach and small intestine were shown to be distended with the presence of both gaseous and aqueous contents. Moreover, caecal contents were impacted and although translucent mucus was prominent, no lesions were seen in the large intestine (Fernández, 2006; Haligur *et al*., 2009; Dewrée *et al.*, 2007).

In addition to the clinical signs mentioned above, this disease is characterized by certain chemical alterations such as secretions of Cl^- ions in the pH of the ileum and colon (Dewrée *et al*., 2007). Interestingly there is a decrease in the pH of the stomach, as well as part of the duodenum and in the urine. This decrease in pH is thought to be due to the lack of food in the stomach, whereas, the increase in pH in the colon is due to microbial dysbiosis (Pérez de Rozas *et al.*, 2005; Bäuerl *et al.*, 2014).

Histologically, there is an inflammatory reaction in the lamina propria; presence of cellular debris and bacteria in the intestinal lumen; presence of apoptotic enterocytes in the crypts and villi; dilation and congestion of the blood vessels in the lamina propria and in the submucosa (Dewrée *et al*., 2007). In addition, there have been reports of edema of the caecal mucosa and submucosa with infiltration of lymphocytes, neutrophil and eosinophil granulocytes and plasma cells, as well as a granulocytic infiltration of the duodenal mucosa (Meshorer, 1976) and hyperplasia of goblet cells. Loss of structure and fusion of proximal colon cells are also reported (Van Kruiningen and Williams, 1972). In studies where the disease was reproduced

with caecal inoculum no lesions have been reported in other organs (e.g. liver, spleen, mesenteric nodes, thymus, heart, kidneys, adrenal gland), apart from those related to corticosteroids, which are used to induce immunosuppression prior to inoculation (Licois *et al*., 1998).

The characteristics of lesions in the small intestine played a major role in the suggestion that the aetiological onset of ERE involved a viral agent to explain the clinical signs (Licois *et al*., 2000). However, this is no longer considered the case as the lesions observed were not specific, with several viruses capable of causing this type of injury or lesions of a similar appearance in rabbits and many other species.

Studies have been undertaken to facilitate the understanding of this syndrome. For example, attempts have been made to perform a ligation of the intestine, following the technique described for the reproduction of shigellosis in rabbits (Arm *et al*., 1965). This involves tying off 15cm segments of the intestinal tract with ligatures and introducing inocula. This resulted in lesions similar to those of mucoid enteritis seen naturally (Cheeke, 1995), with increased β-galactosidase II and decreased β-galactosidase activity relative to healthy animals (Cheeke, 1995). Additionally, there was a decrease in the activity of a number of enzymes, such as cellulase, xylanase and insulinase, which is associated with the microbial change in the natural disease (Bergdall and Dysko, 1994).

Aetiology and spread of ERE.

At present, the aetiology of ERE has not yet been fully elucidated. It is however counted as being very a contagious condition with high morbidities levels, and has mortality values ranging from very low (<10%) to very high (> 80%). Although it is now generally believed that the cause is associated with one or more bacterial species, it was originally suspected to have a nutritional origin, and more recently a viral cause (Licois *et al*., 2000; Boucher, 1998).

ERE is transmitted horizontally via direct oral-faecal (oral grooming) and oral-oral (socialization) contact. This is a reflection of the close contact that exists between animals in nursery productions (Lebas *et al*., 1996).

More recently it has been shown that food was not the primary causal factor, although it may still play a facilitating role (Licois *et al*., 2000; Dewrée *et al*., 2007), with elevated levels in fibre being associated with reduced susceptibility to ERE. For example, the level and type of fibre included in the diet has been shown to have an association with the condition (De Blas *et al*., 2002). Digestive physiological changes associated with the dietary composition arose due to a high amount of soluble carbohydrates and a low amount of fibre increasing the pH of the caecum and decreasing the intestinal transit rate, which in turn has an impact on the microbial population because

it can increase the caecal pH, and promote a greater detection of *Clostridium* spp. (De Blas *et al.*, 2007), increase the production of α-toxins causing damage to the caecal mucosa and aggravating the signs (Romero *et al*., 2011). Also, it has been shown that animals on a high protein diet have a tendency to have more severe and aggravated ERE symptoms (Lleonart, 1990). Recently Jin *et al*. (2018) have reported that low fiber diet leading the incidence of ERE and may develop the disease. However, at the moment it has not been possible to replicate the disease based purely on diet, as attempts to induce ERE purely by dietary changes have been unsuccessful.

Microbiological links to ERE.

The originally described mucoid enteritis was identified as a syndrome of unknown aetiology. More recently, some microorganisms have been shown to be associated with what has been identified as ERE; e.g. *E. coli* O44-K74 and O158-K (Shahin *et al*., 2011), *Haemophilus paracuniculus* (Targowski *et al*., 1979), *Proteus mirabilis, Citrobacter* spp. and *Klebsiella* spp. (McLeod and Katz, 1986).

Additional studies have shown that ERE is characterized by the loss of the few protozoa which may inhabit the tract (mainly coccidial parasites), as well as metachromatic bacilli and other Gram-positive bacteria. In turn, there was an increase in the abundance of Gram negative organisms, acidifying the caecal environment acutely in young rabbits and causing caecal distension and diarrhoea. This triggered hypersecretion of mucus and impaction of the caecal content (Lelkes and Chang, 1987). This was associated with a change in the short chain fatty acid composition in the caecum, with acetate and butyrate decreasing, whilst propionate, isobutyrate, valerate and isovalerate increased, leading to a failure in normal caecal fermentation (Xiccato *et al.*, 2008).

Taking these factors into consideration, it is generally assumed that there is some form of microbial origin associated with the condition. However, from an aetiological perspective, different studies have implicated different microorganisms of the intestinal microbiota. Initial investigations into potential viral origins suggest that although rotaviruses have been observed Licois *et al*. (2000), the infectious agent is unlikely to be a virus (Pérez, 2013), and that bacterial sources are more likely. However, no single species has been reported as being involved in all case studies, although some species have been reported in many studies. These regularly reported organisms include members of the genus *Bacteroides* as well as *Clostridium perfringens* and *Escherichia coli* (Pérez de Rozas *et al*., 2005; Huybens *et al*., 2013; Bäuerl *et al*., 2014). Details of different studies which have been carried out to clarify the causal bacterial species associated with ERE are shown in Table

1, with the number of candidate species listed there demonstrating the difficulties associated with defining an aetiology.

In the case of *Bacteroides* spp. this is made more complicated as these are naturally occurring commensal organisms in the digestive tract. In the broader context, members of the Bacteroidetes phylum have been described throughout the entire digestive tract of both domesticated and wild rabbits (Crowley *et al.*, 2017). While these organisms exist naturally at an equilibrium, it is suspected that an imbalance to their numbers may be associated with ERE, adding to their potential clinical significance (Bäuerl *et al*., 2014; Pérez, 2013; Abecia *et al.*, 2017).

Clostridium perfringens has been observed in the faecal samples of a number of rabbits affected by ERE, with strains of *C. perfringens* having been isolated in 80% of affected animals in Belgium and The Netherlands (Dewrée *et al*., 2007; Huybens *et al*., 2009; Bäuerl *et al*., 2014). In addition, a positive correlation has been reported between the presence of *C. perfringens* alpha toxins and macroscopic lesions typical of ERE. However, attempts to experimentally reproduce ERE following inoculation with strains of *C. perfringens* have been unsuccessful, suggesting that it is not the sole, or possibly even main, agent responsible for the condition (Licois *et al*., 2000; Licois *et al*., 2005; Marlier *et al*., 2006).

Moreover, the potential role of other organisms associated with ERE has been suggested elsewhere in the literature. Licois *et al*. (2000) isolated *Clostridium spiriforme, Clostridium piliforme, Bacillus* spp. and *Escherichia* spp., while other authors have described an increase in certain bacteria such as the genera *Bacteroides*, *Akkermansia*, *Escherichia*, *Rikenella*, *Lysinibacillus* (Bäuerl *et al*., 2014), *Blautia* and *Dorea* (Abecia *et al*., 2017), *Clostridium perfringens, Clostridium spiroforme, Bacteroides fragilis, Akkermansia muciniphila* and *Enterobacter sakazakii* (Jin *et al.*, 2018), as well as individual species such as *Clostridium perfringens, Fusobacterium necrogenes* (Dewree *et al*., 2007), *Streptococcus faecalis* and *Streptococcus faecium* (Szalo *et al*., 2007) in affected animals relative to healthy rabbits.

Table 1. Bacteria which have been suggested to have an association with ERE.

Authors	Associated bacteria	Symptoms used to diagnose ERE	Methods of analysis
Jin *et al.*, 2018	*Clostridium perfringens* and *Clostridium spiroforme, genera Bacteroides fragilis, Akkermansia muciniphila* and *Enterobacter sakazakii*	Anorexia, lethargy, abdominal distension, a hunched posture, caecal impaction and a watery sound in the gut	Illumina MiSeq sequencing
Abecia *et al*., 2017	*Bacteroides* spp. *Blautia* spp. *Dorea* spp. Unclassified clostridia	Abundant faecal mucus	Pyrosequencing
Baüerl *et al*., 2014	*Akkermansia muciniphila* *Bacteroides*/*Prevotella* spp. *Clostridium coccoides* *Methanobrevi bacter*	Apathy Yellow perianal area Translucent mucus	Pyrosequencing
Dewrée *et al*., 2007	*Bacillus* spp. *Clostridium perfringens* *Escherichia coli* *Fusobacterium* spp.	Anorexia Distended abdomen	Necropsy findings Bacterial growth
Huynens *et al*., 2009	*Clostridium* spp. Enterobactericiae spp. *Staphylococcus epidermis*	Bacterial growth Microscopy	Mucus Diarrhoea Death
Marlier *et al.*, 2006	*Clostridium perfringens* *Eimeria* spp. *Escherichia coli*	Caecal impaction Diarrhoea Distended abdomen Mucus	PCR
Rodríguez *et al*., 2008	*Escherichia coli*	Anorexia Caecal impaction Diarrhoea	Bacterial growth Electrophoresis Gamma globulins
Szalo *et al*., 2007	*Bacillus* spp. *Clostridium perfringens* *Fusobacterium* spp. *Streptococcus faecalis* *Streptococcus faecium*	Not specified	Bacterial growth Rotavirus ELISA Microscopy

Experimental reproduction of ERE.

In attempts to better understand this disease, studies have been carried out to reproduce the disease under laboratory conditions. De Blas *et al*. (2007) tried to replicate the disease by modifying the diet. This involved increasing the proportion of dietary protein relative to fibre, as this is believed to favour

the conditions necessary for the disease to occur. However, the symptoms and lesions were not reproduced in the form normally seen in ERE (De Blas *et al.,* 2007).

An alternative approach adopted by Licois *et al*. (2005) involved inoculations with samples from ERE infected animals. Samples used as inocula were third passage material which had been harvested from infected animals and stored at -20˚C for 2 years. This approach proved successful, illustrating that the condition can be replicated by a controlled infection process. This approach was based on Licois *et al*. (1998) and used an unbalanced microbiota, dominated by *Clostridium* spp. primarily *C. perfringens,* containing coccideae and lacking viruses. This resulted in 28% mortality 3 to 6 days post-inoculation and around 50% having cases by 15 days (Licois *et al*., 2005).

More recently, other authors have adopted a similar approach in an effort to reproduce the condition. Purification steps such as differential sucrose gradients (e.g. Szalo *et al.,* 2007) were built in to exclude specific microbial components such as viruses. The results from these approaches support the hypothesis of a bacterial source as the principal factor (Szalo *et al.,* 2007; Huybens *et al.,* 2009), but still could not establish the complete aetiology (Huybens *et al.,* 2011).

Treatment of ERE.

Mortality rates when ERE was first described properly were high (30-80%) (Licois *et al*., 2005; Pérez, 2013) but by the mid-1998, mortality levels began to be controlled, as a result of following strict hygiene and sanitation measures, as well as the use of antibiotics such as bacitracin and tiamulin (Licois *et al*., 2000). By the start of the current century, the most common and efficient way to control ERE in farmed rabbits was by treatment with antibiotics (Dip *et al*., 2015).

As mentioned above, antibiotics are the most commonly used treatment to control ERE, and the best results are achieved when they are not administered orally (De Blas *et al*., 2007; Dip *et al*., 2015), although other research suggests that oral administration may be problematic (Varga *et al*., 2013). While antibiotics are effective in terms of treating ERE, it is also worth noting that some of these can also impact on the microbial population in healthy animals as well. Both bacitracin and tiamulin, which can be used for ERE treatment, have been shown to have a more generalised impact on the microbial community of the rabbit digestive tract (e.g. Abecia *et al*., 2007a; Abecia *et al*., 2007b). Moreover, antibiotic treatment in general has the potential to induce an imbalance in the intestinal microbiota, and ultimately dysbiosis (Lebas *et al*., 1996).

A range of other antibiotics have been used as possible treatments for ERE. However, in some cases they are not used in isolation, but with others at the same as a combination or cocktail of antibiotics e.g. tylosin being used in conjunction with apramycin (de Blas *et al*., 2007). There is however no standard recommended antibiotic for use with ERE cases as, in addition to the ones mentioned previously, other antibiotics such as lincomycin, spectinomycin and neomycin have been used for treatment of ERE (Bäuerl *et al*., 2014).

Conclusion

Although ERE has been studied for over 20 years, and possibly documented for over a century, many factors regarding the condition remain unknown. It now appears clear that the causal organism(s) are bacterial, with a number of candidate species identified as potentially being responsible for the condition, with the likelihood that more than one organism is responsible and that these organisms may work together as a collective infection. Although progress in husbandry and dietary approaches have led to improvements in tackling the problem, the only effective route of tackling an infection continues to rely on antibiotic treatment. In turn, this re-iterates the importance of identifying the principal causal organism(s) and how infection can lead to development of ERE.

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